Closed-Form Formulas for Estimation of Kinetic Parameters in One- and Two-Compartment Models

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Abstract

Nowadays the most reliable approach to estimate the kinetic parameters is to minimize an objective function which is essentially the distance between the measured data and the model generated pseudo data. Due to the highly non-linear nature of the model, common optimization algorithms usually fail to find the true minimum. A brute-force search method sometimes must be used to find the true minimum. This paper attempts to use the Laplace transform and Z-transform methods to derive closed-form formulas for kinetic parameter estimation problems, which assume one- or two-compartment models. The proposed method is computationally efficient and its solution is unique. When data sampling interval is small, the proposed method is able to accurately estimate the kinetic parameter; when the interval is larger, the proposed method fails to give a meaningful estimate. The one-compartment method is more robust than the two-compartment method.

I. Introduction

Here we use a one-compartment model (see Fig. 1) with two kinetic parameters, K_1 and k_2, to review some current methods in kinetic parameter estimation. The one-compartment model can be mathematically described as a first-order differential equation:

$$\frac{dC(t)}{dt} = K_1 B(t) - k_2 C(t), \tag{1}$$

where $B(t)$ is the given input function and $C(t)$ is the measured data.

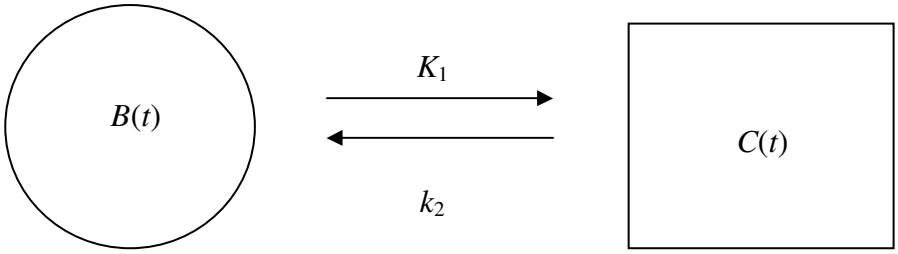

Figure 1. A general single-tissue-compartmental-model.

If we solve the differential equation (1) for $C(t)$, we obtain

$$C(t) = K_1 \int_0^t e^{-k_2(t-\tau)} B(\tau) d\tau . \tag{2}$$

Expression (2) is commonly used to estimate K_1 and k_2 by non-linear fitting methods by minimizing the objective function:

$$\chi^2 = \left\| C(t) - K_1 \int_0^t e^{-k_2(t-\tau)} B(\tau) d\tau \right\|^2 . \tag{3}$$

Currently this approach is the most reliable one [1]-[3]. However, in a two-compartment model or multi-compartment model, the objective function is highly non-linear. It is difficult to use a common optimization algorithm to search for its true minimum. A brute-force search sometimes is the only reliable method to find the true minimum, but a brute-force search can be time consuming in some large data set applications. It will have a significant impact if an efficient, closed-form solution available for a multi-compartment model kinetic parameter estimation problem.

To find a closed-form solution using a computer needs to convert the original differential equation into an algebraic equation or a difference equation, because one cannot directly implement d$C(t)$/dt without any approximation.

One way to solve for K_1 and k_2 is to discretize (1) as,

$$\frac{C(nT) - C(nT - T)}{T} \approx K_1 B(nT - T) - k_2 C(nT - T), \tag{4}$$

where is T is a sampling interval. The approximation in (4),

$$\frac{dC(t)}{dt} \approx \frac{C((n+1)T) - C(nT)}{T}, \tag{5}$$

is rather poor for practical sampling interval T and thus the resultant estimation of K_1 and k_2 contains large errors.

Another approach is to integrate the both sides of (1), and this yields

$$C(t) = K_1 \int_0^t C(\tau) d\tau - k_2 \int_0^t B(\tau) d\tau . \tag{6}$$

Notice that $\int_0^t C(\tau) d\tau$ is the image value reconstructed with all projections acquired in time interval [0, t] and $C(t)$ is the image value reconstructed with projections acquired at time instant t . In practice, it is not realistic to obtain $C(t)$. The numeric calculation of $\int_0^t B(\tau) d\tau$ may introduce a large error over such a large time interval if the analytical form of $B(t)$ is not known. Some modern kinetic parameter estimation methods [4]-[6] are based on the linear model (6).

As a pre-view, a main result in this paper is to transform the differential equation (1) into a difference equation:

$$2[C(t) - C(t-T)] = k_2 T \{ g_{dc} [B(t) + B(t-T)] - [C(t) + C(t-T)] \} \tag{7}$$

where g_{dc} is the DC gain from $B(t)$ to $C(t)$ and $K_1 = g_{dc}\, k_2$. Equation (7) is obtained by using a bilinear transformation that relates the Laplace transform to the Z-transform. This approach is more accurate than the approximation in (5). In (7), the values C and B can be the instant values and can also be integrated values over a time interval.

The relationship between the continuous-time signal's Laplace transform with the variable s and the discrete-time signal's Z-transform with the variable z is essentially $z = e^{sT}$ where T is the sampling interval. In the Laplace domain, s corresponds to the derivative operator in the time domain. In the z domain, z^{-1} corresponds to the unit delay in the time domain. In order to see that the bilinear transformation is a more accurate approximation than (5), let us compare the following three Taylor expansions:

$$z^{-1} = e^{-sT} = 1 - sT + \frac{(sT)^2}{2!} - \frac{(sT)^3}{3!} + \frac{(sT)^4}{4!} - \ldots \tag{8}$$

$$z^{-1} = e^{-sT} \approx 1 - sT \tag{9}$$

$$z^{-1} = e^{-sT} \approx \frac{1 - sT/2}{1 + sT/2} = 1 - sT + \frac{(sT)^2}{2} - \frac{(sT)^3}{2^2} + \frac{(sT)^4}{2^3} - \ldots \tag{10}$$

Equation (8) is the exact Taylor expansion of e^{-sT}, equation (9), which implies the transformation $s = (1 - z^{-1})/T$, is equivalent to (5), and equation (10) is equivalent to the bilinear transformation, $s = (2/T)(1 - z^{-1})/(1 + z^{-1})$, that will be used in this paper to derive closed-form formulas for kinetic parameter estimation. Clearly, (10) is more accurate than (9) to approximate (9).

II. Derivation of the closed-form formulas

Figures 1 and 2 show generic one and two compartment models, respectively. The circle in the figures represents the input function, and the squares represent the compartments in the tissue. The single compartment model in Fig. 1 has only one compartment in tissue and exchanges tracer between plasma compartment $B(t)$ and tissue compartment $C(t)$ by two rate constants K_1 and k_2. The two-compartment model of the tissue in Fig. 2 has four rate constants: K_1, k_2, k_3 and k_4. In the following, we will develop some mathematical formulas for these two models, respectively.

II. A. One-compartment model formulas

The differential equation for the one-compartment model can be written as

$$\frac{dC(t)}{dt} = K_1 B(t) - k_2 C(t). \tag{11}$$

Taking the Laplace transform of this equation, we have

$$s\tilde{C}(s) = K_1 \tilde{B}(s) - k_2 \tilde{C}(s), \tag{12}$$

which immediately gives the transfer function $\tilde{H}(s)$ of the system as

$$\tilde{H}(s) = \frac{\tilde{C}(s)}{\tilde{B}(s)} = \frac{K_1}{s + k_2}. \tag{13}$$

Letting s=0 yields the DC gain of the system

$$\text{DC gain } g_{dc} = \frac{\tilde{C}(0)}{\tilde{B}(0)} = \frac{K_1}{k_2}. \tag{14}$$

In practice, the DC gain g_{dc} can be readily obtained as the ratio of the total sum (i.e., integral) of the function $C(t)$ over the total sum (i.e., integral) of the function $B(t)$.

When measurements are processed in a computer, a continuous-time system needs to be approximated by a discrete-time system. One way of performing this conversion is via the Laplace transform to Z-transform conversion. The relationship between s and z is given as

$$z = e^{sT} \tag{15}$$

where T is the sampling interval. From (15), s can be expressed by z as

$$s = \frac{1}{T}\ln z = \frac{2}{T}\left[\frac{1-z^{-1}}{1+z^{-1}} + \frac{1}{3}\left(\frac{1-z^{-1}}{1+z^{-1}}\right)^3 + \frac{1}{5}\left(\frac{1-z^{-1}}{1+z^{-1}}\right)^5 + \ldots\right] \approx \frac{2}{T}\frac{1-z^{-1}}{1+z^{-1}}. \tag{16}$$

The bilinear transformation

$$s = \frac{2}{T}\frac{1-z^{-1}}{1+z^{-1}} \tag{17}$$

is popular in the field of digital signal processing, because it transforms a rational transfer function in the Laplace domain into a rational transfer function in the Z-domain. As seen in (16), when the sampling interval T is small, a continuous-time system can be accurately approximated by its discrete-time counterpart via the bilinear transformation. However, when T is large, the approximation is poor.

Using the bilinear transformation (17), the continuous-time system (13) is transformed into

$$\frac{\hat{C}(z)}{\hat{B}(z)} = \frac{K_1}{\frac{2}{T}\frac{1-z^{-1}}{1+z^{-1}} + k_2} = \frac{K_1 T(1+z^{-1})}{2(1-z^{-1}) + k_2 T(1+z^{-1})}. \tag{18}$$

Combining (14) and (18) yields

$$2(1-z^{-1})\hat{C}(z) = k_2 T[g_{dc}(1+z^{-1})\hat{B}(z) - (1+z^{-1})\hat{C}(z)]. \tag{19}$$

Taking the inverse Z-transform and realizing that z^{-1} means a delay of T, we obtain a time-domain expression:

$$D(t) = k_2 E(t) \tag{20}$$

with t now taking discrete values and

$$D(t) = 2[C(t) - C(t-T)] \tag{21}$$

$$E(t) = T\{g_{dc}[B(t) + B(t-T)] - [C(t) + C(t-T)]\}. \tag{22}$$

Calculating dot products with $E(t)$ on both sides of (20) gives

$$\langle D(t), E(t)\rangle = k_2 \langle E(t), E(t)\rangle. \tag{23}$$

Finally, the estimated kinetic parameters are obtained with the closed-form expressions

$$\begin{cases} k_2 = \dfrac{\langle D(t), E(t)\rangle}{\langle E(t), E(t)\rangle} \\ K_1 = g_{dc} k_2. \end{cases} \tag{24}$$

II. B. Two-compartment model formulas

Two differential equations for the two-compartment model can be written as

$$\frac{dC_1(t)}{dt} = (-k_2 - k_3)C_1(t) + k_4 C_2(t) + K_1 B(t), \tag{25}$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t) - k_4 C_2(t). \tag{26}$$

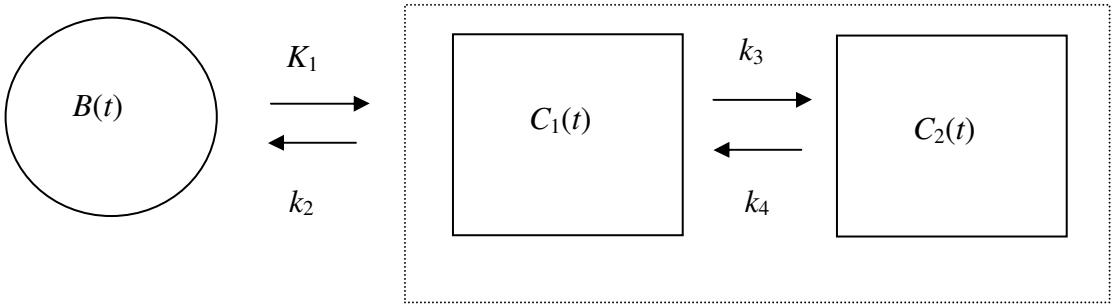

Figure 2. A general two-tissue-compartmental-model.

The above two equations are referred to as the state equations in system theory. The compartments $C_1(t)$ and $C_2(t)$ are not accessible; however, the sum of them, $C(t)$ defined as

$$C(t) = C_1(t) + C_2(t)\,, \tag{27}$$

can be measured. Equation (27) is called the output equation in system theory. By taking the Laplace transform of (25), (26), and (27), we have

$$s\tilde{C}_1 = (-k_2 - k_3)\tilde{C}_1(s) + k_4\tilde{C}_2(s) + K_1\tilde{B}(s)\,, \tag{28}$$

$$s\tilde{C}_2(s) = k_3\tilde{C}_1(s) - k_4\tilde{C}_2(s)\,, \tag{29}$$

$$\tilde{C}(s) = \tilde{C}_1(s) + \tilde{C}_2(s)\,. \tag{30}$$

Solving for $\tilde{C}_1(s)$ and $\tilde{C}_2(s)$ from (28) and (29) then substituting them into (30), we obtain the output/input ratio $\tilde{C}(s)/\tilde{B}(s)$ in the Laplace domain, which is the transfer function of the system:

$$\tilde{H}(s) = \frac{\tilde{C}(s)}{\tilde{B}(s)} = K_1 \cdot \frac{s + (k_3 + k_4)}{s^2 + (k_2 + k_3 + k_4)s + k_2k_4}\,. \tag{31}$$

Letting s=0 in (31) yields the DC gain of the system

$$\text{DC gain } g_{dc} = \frac{\tilde{C}(0)}{\tilde{B}(0)} = \frac{K_1(k_3 + k_4)}{k_2k_4}\,. \tag{32}$$

In practice, the DC gain g_{dc} can be readily obtained as the ratio of the total sum (i.e., integral) of the function $C(t)$ over the total sum (i.e., integral) of the function $B(t)$.

After performing the bilinear transformation (17), an approximate discrete-time counterpart is obtained as

$$\frac{\hat{C}(z)}{\hat{B}(z)} = K_1 \cdot \frac{\frac{2}{T}\frac{1-z^{-1}}{1+z^{-1}} + (k_3 + k_4)}{(\frac{2}{T}\frac{1-z^{-1}}{1+z^{-1}})^2 + (k_2 + k_3 + k_4)\frac{2}{T}\frac{1-z^{-1}}{1+z^{-1}} + k_2k_4}\,. \tag{33}$$

Taking the inverse Z-transform of (33) and using the DC gain relation (32), we have a time-domain model:

$$F(t) = x_1G(t) + x_2L(t) + x_3M(t) \tag{34}$$

where t now takes discrete values and

$$F(t) = 4[C(t) - 2C(t-T) + C(t-T)] \tag{35}$$

$$G(t) = T^2\{g_{dc}[B(t) + 2B(t-T) + B(t-2T)] - [C(t) + 2C(t-T) + C(t-2T)]\} \tag{36}$$

$$L(t) = 2T[B(t) - B(t-2T)] \tag{37}$$

$$M(t) = -2T[C(t) - C(t-2T)] \tag{38}$$

$$x_1 = k_2k_4 \tag{39}$$

$$x_2 = k_2 + k_3 + k_4 \tag{40}$$

$$x_3 = K_1\,. \tag{41}$$

Let $x_4 = K_1(k_3 + k_4)$. The DC gain relationship (32) implies $x_4 = g_{dc}x_1$. In order to solve for the three unknowns in (34), x_1, x_2, and x_3, (34) must first be transformed into a system of three equations. One can choose three functions, say, $U_1(t)$, $U_2(t)$, and $U_3(t)$, to calculate inner products with (34) and obtain three linear equations:

$$\begin{cases} \langle F(t),U_1(t)\rangle = x_1\langle G(t),U_1(t)\rangle + x_2\langle L(t),U_1(t)\rangle + x_3\langle M(t),U_1(t)\rangle \\ \langle F(t),U_2(t)\rangle = x_1\langle G(t),U_2(t)\rangle + x_2\langle L(t),U_2(t)\rangle + x_3\langle M(t),U_2(t)\rangle \\ \langle F(t),U_3(t)\rangle = x_1\langle G(t),U_3(t)\rangle + x_2\langle L(t),U_3(t)\rangle + x_3\langle M(t),U_3(t)\rangle \end{cases} \tag{42}$$

With carefully chosen $U_1(t)$, $U_2(t)$, and $U_3(t)$, the three equations in (42) are linear independent and the unknowns, x_1, x_2, and x_3, can be readily obtained by inverting a 3x3 matrix and multiplying a 3x1 column vector:

$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} = \begin{bmatrix} \langle G(t),U_1(t)\rangle & \langle L(t),U_1(t)\rangle & \langle M(t),U_1(t)\rangle \\ \langle G(t),U_2(t)\rangle & \langle L(t),U_2(t)\rangle & \langle M(t),U_2(t)\rangle \\ \langle G(t),U_3(t)\rangle & \langle L(t),U_3(t)\rangle & \langle M(t),U_3(t)\rangle \end{bmatrix}^{-1} \begin{bmatrix} \langle F(t),U_1(t)\rangle \\ \langle F(t),U_2(t)\rangle \\ \langle F(t),U_3(t)\rangle \end{bmatrix}. \tag{43}$$

Finally, the estimated kinetic parameters are obtained with the closed-form expressions

$$\begin{cases} K_1 = x_3 \\ k_2 = x_2 - x_4 / x_3 = x_2 - g_{dc} x_1 / x_3 \\ k_4 = x_1 / k_2 \\ k_3 = x_4 / x_3 - k_4 = g_{dc} x_1 / x_3 - k_4 \end{cases} \tag{44}$$

One has freedom to choose the functions $U_1(t)$, $U_2(t)$, and $U_3(t)$. After a few trials, we found that the selection of functions $U_1(t)$, $U_2(t)$, and $U_3(t)$ can affect the robustness of the solution, and we chose $U_1(t) = B(t)$, $U_2(t) = C(t)$, and $U_3(t)$ to be a cosine function whose period is the entire signal duration.

III. Comments on the Theory

III. A. Summed measurements vs. sampled measurements

In dynamic SPECT and PET, the measurements do not correspond to sampled values of a continuous time-activity curve (TAC), but rather to the integrated TAC values over a time interval: either [t-T, T] or [0, t]. Integrated data are equivalent to first filtering the continuous TAC data with a boxcar kernel, then sampling this low-pass filtered TAC at different time instants.

Let us consider the situation that the TAC data are integrated over the time interval [t-T, T]. The relationship expressed by (34) holds for continuous functions; we can integrate the both sides of (34) over the time interval [t-T, T], obtaining the exactly same expression except that $C(t)$, $C(t\text{-}T)$, $C(t\text{-}2T)$, $B(t)$, $B(t\text{-}T)$, and $B(t\text{-}2T)$ in (35)-(38) are replaced by their integrated (i.e., low-pass filtered) counterparts. Therefore, the proposed methodology can be applied to general function forms, which can be continuous-time signal, discrete-time sampled signal, signal that has been integrated over an arbitrary time interval.

III. B. Extension to multi-compartment models

In general, if we have N compartments for the tissue model, we have a system of N first-order differential equations (which are called state equations) to describe the kinetics. Let $\vec{C}$ be a vector that contains all N compartments, A be an NxN matrix, D be an Nx1 matrix and E be a 1xN matrix. The system of differential equations can be expressed in a matrix form

$$\frac{d\vec{C}(t)}{dt} = A\vec{C}(t) + DB(t)\,. \tag{45}$$

The measurable activity is described by the output equation:

$$C(t) = E\vec{C}(t)\,, \tag{46}$$

where the $C(t)$ on the left-hand-side is a scalar. Using the Laplace transform, the system's transfer function can be obtained as

$$\tilde{H}(s) = \frac{\tilde{C}(s)}{\tilde{B}(s)} = E(sI - A)^{-1}D = \frac{\gamma_{N+1} + \gamma_{N+2}s + \ldots + \gamma_{N+N}s^{N-1}}{s^N - \gamma_1 s^{N-1} - \ldots - \gamma_{N-1}s - \gamma_N}\,. \tag{47}$$

By taking the bilinear transformation, (47) can be converted into

$$P_0(t) = \gamma_1 P_1(t) + \gamma_2 P_2(t) + \ldots + \gamma_{2N} P_{2N}(t) \tag{48}$$

where $P_i(t)$ consists of $C(t)$, $C(t\text{-}T)$, $C(t\text{-}2T)$, …, $C(t\text{-}NT)$, $B(t)$, $B(t\text{-}T)$, $B(t\text{-}2T)$, …, $B(t\text{-}NT)$, i = 1, 2, …, 2N. Using the DC gain of the system

$$\text{DC gain } g_{dc} = \frac{\tilde{C}(0)}{\tilde{B}(0)} = -\frac{\gamma_{N+1}}{\gamma_N}\,. \tag{49}$$

and a set of user-chosen functions $U_1(t)$, $U_2(t)$, …, $U_{2N\text{-}1}(t)$, a system of 2N-1 independent linear equations (similar to (42)) can be formed and the unknowns (γ_i) can be solved. The γ_i's are directly related to the kinetic parameters, and the kinetic parameters are finally obtained.

III. C. Consideration of the input function contamination effect

In the above discussion, we assume that the quantity $C(t)$ can be measured. In reality, the measured $C(t)$ can be contaminated by the input function $B(t)$. The system's transfer function (31) should be revised to reflect this effect as

$$\begin{aligned}\tilde{H}_{revised}(s) &= (1-f_v)K_1 \cdot \frac{s+(k_3+k_4)}{s^2+(k_2+k_3+k_4)s+k_2k_4} + f_v \\ &= \frac{f_v s^2 + [(1-f_v)K_1 + f_v(k_2+k_3+k_4)]s + [(1-f_v)K_1(k_3+k_4) + f_v k_2 k_4]}{s^2+(k_2+k_3+k_4)s+k_2k_4}.\end{aligned} \tag{50}$$

This revised transfer function has an extra s^2 term on the nominator. We still can use the same procedure proposed in Section II to solve the unknowns and we have an extra unknown. The DC gain is modified accordingly as

$$\text{DC gain } g_{dc} = \frac{\tilde{C}(0)}{\tilde{B}(0)} = \frac{(1-f_v)K_1(k_3+k_4) + f_v k_2 k_4}{k_2 k_4}. \tag{51}$$

IV. Results

IV.A. Input function and measurement generation

In computer simulations, the blood input functions were in the form of [6]

$$B(t) = (A_1 t - A_2 - A_3)e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + A e^{-\lambda_3 t}\ ,\ t \geq 0\,, \tag{52}$$

where A_1 = 21.28, A_2 = 7.71, A_3 = 0.37, λ_1 = 2.0 min^{-1}, λ_2 = 1.0 min^{-1}, and λ_3 = 0.1 min^{-1}. The blood time activity curve was assumed to be noiseless and sampling intervals T were chosen as 1 second, 2 seconds, and 5 seconds, respectively. The simulated data acquisition time was 135 minutes.

It is important to point out that the measurement $C(t)$ was analytically generated with a mathematically exact convolution formula. Scaled Gaussian noise $N(0,1)$ (mean=0, standard deviation=1) was added to the noiseless data $C(t)$, and the noise scaling factor was

$$\alpha\sqrt{\frac{C(t)}{T(second)}}\,. \tag{53}$$

where the proportional constant α = 0.0, 0.1, 0.2 and 0.4, respectively, for different noise levels.

IV. B. One-compartment model examples

The compartment time-activity-curve $C(t)$ was generated with K_1 = 0.4 min^{-1} and k_2 = 0.2 min^{-1}. Typical noisy time activity curves $C(t)$ are shown in Figure 3 for four α values. In the computer simulations, 1000 runs were used for each noise level. The mean values and the standard deviations for the estimated kinetic parameters K_1 and k_2 are listed in Table 1. A Gaussian convolution kennel was used to convolve both $B(t)$ and $C(t)$ for low-pass filtering before parameter estimation method was applied. The computation times reported in Tables 1 and 2 are for 1000 noise trials, and the algorithm was coded and run in MATLAB®.

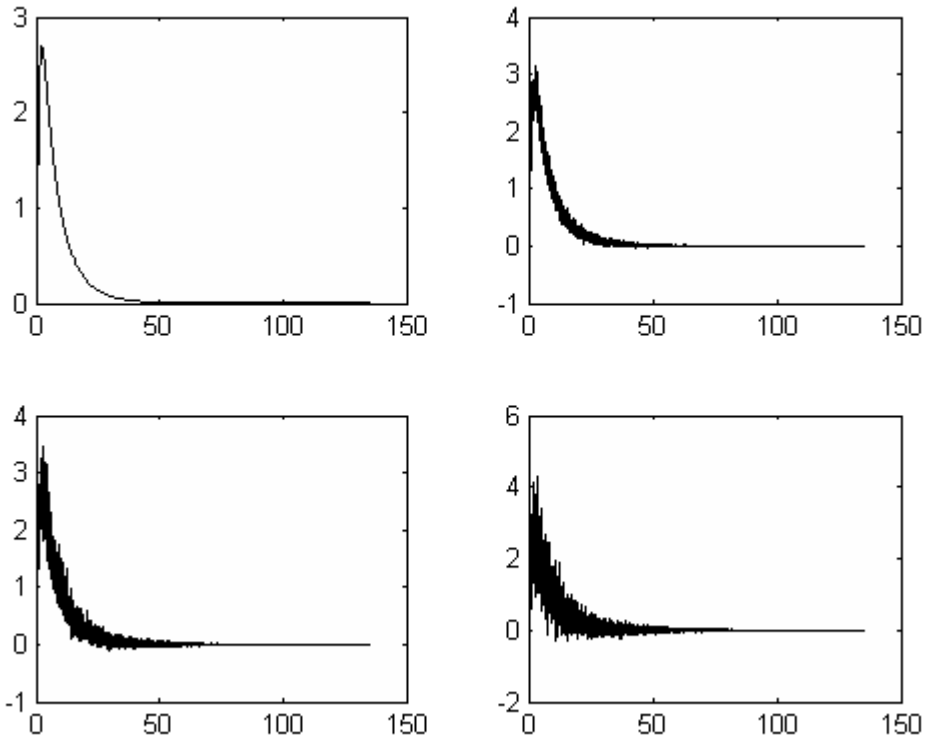

Figure 3. [One-Compartment Model] Time-activity curves $C(t)$ with different noise levels: upper left $\alpha = 0$, upper right $\alpha = 0.1$, lower left $\alpha = 0.2$, lower right $\alpha = 0.4$. The horizontal axis is time (in minutes).

TABLE 1. Estimation Results for the One-Compartment Model Parameters K_1 and k_2

Data sampling time T (seconds)	Noise level α	K_1 (min^{-1})	k_2 (min^{-1})	Computation time for 1000 noise trials (seconds)
1	0.0	0.40	0.20	
	0.1	0.40±0.0047	0.20±0.0023	6
	0.2	0.40±0.0093	0.20±0.0045	
	0.4	0.40±0.0191	0.20±0.0093	
2	0.0	0.40	0.20	
	0.1	0.40±0.0050	0.20±0.0025	4
	0.2	0.40±0.0100	0.20±0.0048	
	0.4	0.40±0.0201	0.20±0.0099	
5	0.0	0.40	0.20	
	0.1	0.40±0.0029	0.20±0.0013	3
	0.2	0.40±0.0055	0.20±0.0026	
	0.4	0.42±0.0114	0.20±0.0053	
True values		**0.40**	**0.20**	

IV. C. Two-compartment model examples

The compartment time-activity-curve $C(t)$ was generated with $K_1 = 0.4$ min^{-1}, $k_2 = 0.3$ min^{-1}, $k_3 = 0.2$ min^{-1} and $k_4 = 0.1$ min^{-1}. Typical noisy time activity curves $C(t)$ are shown in Figure 4 for four α values. A Gaussian convolution kennel was used to convolve both $B(t)$ and $C(t)$ for low-pass filtering before parameter estimation method was applied. In the computer simulations, 1000 runs were used for each noise level. The mean values and the standard deviations for the estimated kinetic parameters $K_1 \sim k_4$ are listed in Table 2.

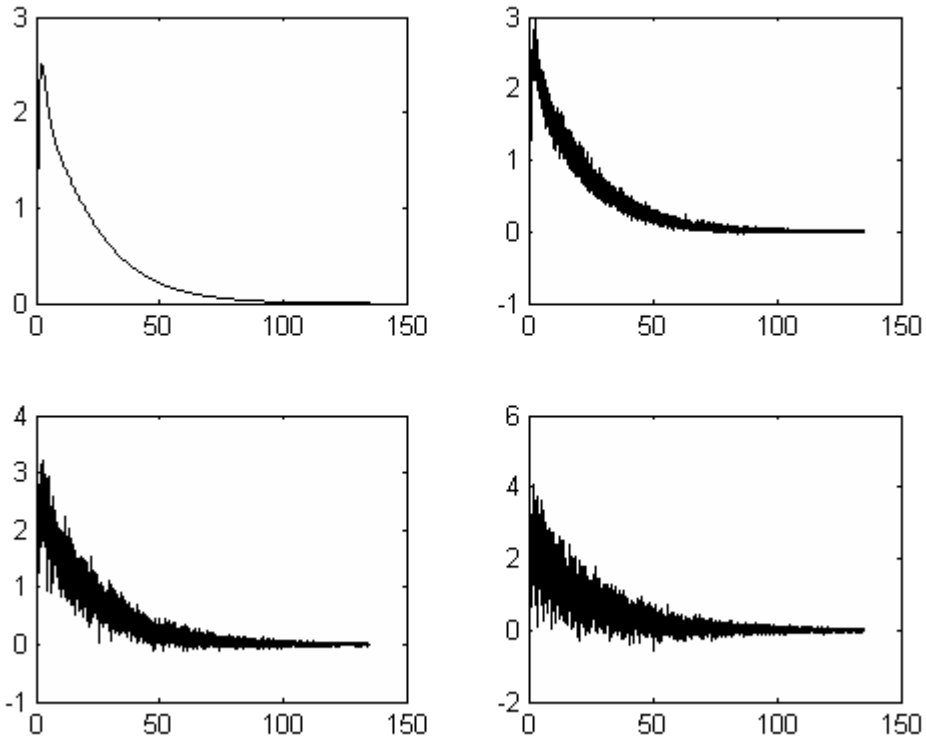

Figure 4. [Two-Compartment Model] Time-activity curves $C(t)$ with different noise levels: upper left $\alpha = 0$, upper right $\alpha = 0.1$, lower left $\alpha = 0.2$, lower right $\alpha = 0.4$. The horizontal axis is time (in minutes).

TABLE 2. Estimation Results for the Two-Compartment Model Parameters K_1, k_2 , k_3, and k_4

Data sampling time T (seconds)	Noise level α	K_1 (min^{-1})	k_2 (min^{-1})	K_3 (min^{-1})	K_4 (min^{-1})	Computation time for 1000 noise trials (seconds)
1	0.0	0.40	0.30	0.20	0.10	
	0.1	0.40±0.0163	0.30±0.0306	0.20±0.0179	0.10±0.0028	24
	0.2	0.40±0.0325	0.29±0.0592	0.18±0.0372	0.10±0.0061	
	0.4	0.38±0.0623	0.26±0.0993	0.13±0.0675	0.08±0.0247	
2	0.0	0.41	0.31	0.20	0.10	
	0.1	0.41±0.0306	0.31±0.0430	0.20±0.0120	0.10±0.0063	17
	0.2	0.41±0.0651	0.31±0.0920	0.19±0.0258	0.10±0.0165	
	0.4	0.39±0.1353	0.28±0.1967	0.16±0.9074	0.12±0.9076	
5	0.0	0.41	0.31	0.20	0.10	
	0.1	0.01±11.37	-0.23±15.13	0.32±4.937	-0.02±4.938	12
	0.2	-0.01±9.386	-0.38±13.32	0.33±1.067	0.02±0.9729	
	0.4	0.24±4.332	0.03±6.551	0.40±2.363	-0.01±0.6646	
True values		**0.40**	**0.30**	**0.20**	**0.10**	

It is observed in TABLE 2 that when the sampling interval T is 5 seconds and there is noise, the proposed algorithm only produces nonsense. We tried to improve the approximation accuracy of (16) by using two terms, that is,

$$s = \frac{1}{T}\ln z \approx \frac{2}{T}[\frac{1-z^{-1}}{1+z^{-1}} + \frac{1}{3}(\frac{1-z^{-1}}{1+z^{-1}})^3]. \tag{54}$$

We repeated the results in TABLE 2, obtaining TABLE 3. Unfortunately, this improved approximation (54) did not give us much better results that those in TABLE 2.

TABLE 3. [two-term bilinear] Estimation Results for the Two-Compartment Model Parameters K_1, k_2 , k_3, and k_4

Data sampling time T (seconds)	Noise level α	K_1 (min^{-1})	k_2 (min^{-1})	K_3 (min^{-1})	K_4 (min^{-1})	Computation time for 1000 noise trials (seconds)
1	0.0	0.40	0.30	0.20	0.10	
	0.1	0.40±0.0156	0.30±0.0298	0.20±0.0179	0.10±0.0026	25
	0.2	0.40±0.0317	0.29±0.0581	0.18±0.0353	0.10±0.0055	
	0.4	0.39±0.0652	0.27±0.1070	0.14±0.0689	0.08±0.0235	
2	0.0	0.41	0.31	0.20	0.10	
	0.1	0.41±0.0288	0.31±0.0417	0.20±0.0115	0.10±0.0057	17
	0.2	0.41±0.0578	0.31±0.0819	0.19±0.0252	0.10±0.0155	
	0.4	0.40±0.1542	0.30±0.2488	0.11±1.105	0.16±1.100	
5	0.0	0.39	0.29	0.20	0.10	
	0.1	-0.12±14.92	-0.44±21.13	0.28±2.641	0.03±2.640	13
	0.2	0.47±18.46	0.31±24.99	0.17±2.053	0.13±2.031	
	0.4	0.26±2.659	0.10±4.716	0.39±4.146	-0.06±3.456	
True values		**0.40**	**0.30**	**0.20**	**0.10**	

V. Conclusions

Time-domain curve-fitting is the current state-of-the-art in nuclear medicine kinetic estimation. Due to the non-linear exponential functions, this curve-fitting is sensitive to noise, especially for multi-compartment model parameter estimation problems. The noise may make the algorithm converge to a wrong solution; therefore it is unreliable to use a common optimization algorithm to perform curve fitting. In this paper, a closed-form kinetic estimation method is proposed, attempting to provide a unique solution in a fast. The proposed method is based on the bilinear transformation that converts the Laplace-domain system transfer function into a Z-domain system transfer function. The purpose of this conversion is to change the derivative operator to the finite difference operator so that it is possible to be implemented on a computer. This bilinear transformation is a more accurate approximation than the simple difference.

Computer simulations reveal that the proposed estimation algorithm is relatively robust against noise for the one-compartment model. In a two-compartment model, the performance is rather poor when the sampling time-interval is not small enough and the data are corrupted with noise. Using a small sampling interval is equivalent to using a slow changing input function. The bolus administration should be slow and gentle.

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